THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 01.04.2002 in respect of Patent Application No. 310/MUM/2002 of Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad-380 015, Gujarat, India.

This certificate is issued under the powers vested on me under Section 147 (1) of the Patents Act, 1970.

Dated this 1st day of May 2003

(N. K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED,** a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

'NOVEL ANTIINFECTIVE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM '

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

ORIGINAL

(3) Further declare that the true and first inventor for the said invention is ,

Brijesh Kumar SRIVASTAVA, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: NIL

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
Patent and Trademark Attorneys
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Fax: 91 11 628 6005
Email: sna@vsnl.com

310/MUM/2002
Dated. 1/4/2002

(7) Following declaration was given by the inventor

I, **Brijesh Kumar SRIVASTAVA**, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventor for this invention declare that the applicants herein is my assignees.

BKumar.

Brijesh Kumar SRIVASTAVA

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
- (a) Provisional specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f)- Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 30th day of March , 2002

The Controller of Patents
The Patent Office,
At Mumbai

for CADILA HEALTHCARE LIMITED
(name and designation of signatory)

ZRC-MC-007
FORM 2

The PATENT ACT, 1970
(39 of 1970)
Provisional Specification

DUPLICATE

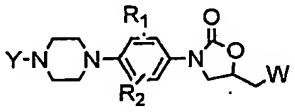
NOVEL ANTIINFECTIVE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

CADILA HEALTH CARE LTD
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway, Ahmedabad-380015, Gujarat, India

The following specification describes the nature of the invention and the manner in which it is to be performed:

Field of Invention

The present invention relates to novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts and pharmaceutical compositions containing them. The present invention also relates to a process of preparing compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.



(I)

The compounds of the present invention are useful in the treatment of a number of human and veterinary pathogens, including aerobic as well as anaerobic Gram-positive and Gram-negative organisms.

Background to the invention

Antibiotic resistance is a serious concern worldwide as it would result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention though being primarily effective against Gram-positive pathogens are also effective against certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and Mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus(MRSA),

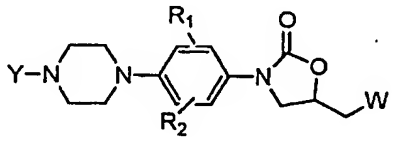
methicillin resistant coagulase negative staphylococci(MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium* and so on.

Antibacterial agents containing an oxazolidinone ring have been described in J. Med. Chem. 1992, 35, 2569-78 (Gregory W. A. et. al) and J Med. Chem. 1992, 35, 1156-65 (Chung-Ho Park et. al). Also, US 4705799 and 5523403 and EP0316594 disclose substituted phenyl-2-oxazolidinones. US 4948801, 5254577 & 5130316 discloses arylbenzene oxazolidinyl compounds including substituted or unsubstituted phenyl and pyridyl groups. Heteroaryl-oxazolidinones having one to three atoms selected from the group consisting of oxygen, sulfur, nitrogen and oxygen are described in EP 0697412, 0694544, 0694543 & 0693491. Further, oxazolidinone derivatives useful as antibacterial agents are described in WO 0181350, WO 0032599, WO 9807708, WO 9730981, WO 9721708, WO 9710235, WO 9709328, WO 9719089, WO 9710223, WO 9615130, WO 9613502, WO 9514684, WO 9507271, WO 9413649, WO9323384, WO 9002744, US 4801600, US 4921869, EP 0353781, EP 0316594 etc.

Due to increase in antibiotic resistance there is a continuous need to develop more effective medicines suitable against such pathogenic organisms.

Summary of the invention

The present invention describes a group of novel compounds useful as antibacterial agents. The novel compounds are defined by the general formula (I) below:



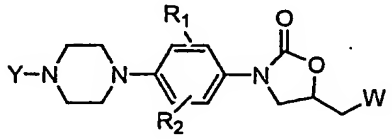
(I)

The compounds of the present invention are useful in the treatment of the human or animal body, as preventives and therapeutics for infectious diseases. The compounds of this invention have excellent antimicrobial action against various human and veterinary pathogens including but not limited to multiply-resistant staphylococci and streptococci, as well as anaerobic organisms including those of the bacteroides and clostridia species, and acid-fast

Mycobacterium tuberculosis and *Mycobacterium avium* with better efficacy, potency and minimum toxic effects.

Objectives :

The main objective of the present invention thus is to provide novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures suitable in the treatment of infectious diseases.



(I)

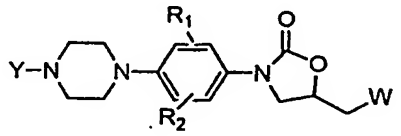
Another objective of the present invention is to provide a process for the preparation of novel compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, novel intermediates involved in their synthesis pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

Yet another objective of the present invention is to provide pharmaceutical compositions containing compounds of general formula (I), their analogs, their derivatives, their stereoisomers, their tautomeric forms, their pharmaceutically acceptable salts, solvates and their mixtures having pharmaceutically acceptable carriers, solvents, diluents and other media normally employed in their manufacture.

Still another objective of the present invention is to provide a method of treatment of antibiotic resistant pathogens, by administering a therapeutically effective & non-toxic amount of the compound of formula (I) or their pharmaceutically acceptable compositions to the mammals.

Detailed Description of the description

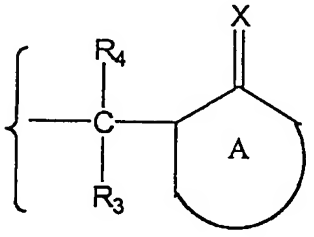
The novel compounds of the present invention are defined by the general formula (I) below:



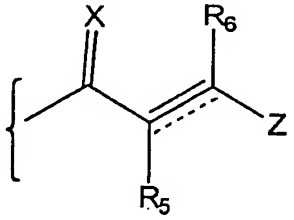
(I)

Where R_1 & R_2 may be same or different and represents hydrogen, halogens, substituted or unsubstituted groups selected from alkyl, aralkyl, haloalkyl groups;

Y represents:

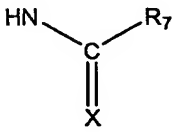


or



where R_3 , R_4, R_5 & R_6 may be same or different and represents H, C_1-C_6 substituted or unsubstituted alkyl group; X represents O, S or NR^8 where R^8 represents H or (un)substituted alkyl groups; A represents a (un)substituted, saturated or unsaturated or partially saturated single or fused ring moiety, optionally containing one or more heteroatoms selected from N, S, O; Z represents optionally substituted or unsubstituted groups selected from alkyl, alicyclic, aryl, heteroaryl or heterocyclic groups.

W is defined by the general form:



Wherein R_7 may be H, substituted or unsubstituted groups selected from amino, alkylamino, dialkylamino, aralkylamino, alkoxy, thioalkoxy, and X is selected from O, S, $-NR_8$ where R_8 represents H, or substituted or unsubstituted alkyl group.

Suitable substituents on groups A & Z may be selected from cyano, nitro, halo, perhaloalkyl, carboxyl, hydrazino, azido, formyl, amino, thio, hydroxy, sulfonyl, or substituted or unsubstituted groups selected from alkyl which may be linear or branched; alkenyl, cycloalkenyl, hydrazinoalkyl, alkylhydrazido, hydroxylamino, acyl, acyloxy, acylamino, carboxyalkyl, haloalkyl, aminoalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylaminoalkyl, arylamino, aralkylamino, aralkoxy, haloaralkyl, aralkenyl, aryl, aralkyl, aryloxy, alkoxy, carbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylcarbonylalkyl, alkoxycarbonylalkyl, amidino, carboxamidoalkyl, cyanoamidino, cyanoalkyl, aminocarbonylalkyl, N-aminocarbonylalkyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, carboxyalkylaminocarboxy, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-aralkyl-N-alkylaminoalkyl, N-alkyl-N-arylaminoalkyl, N-N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-hydroxyaminocarbonyl, N-alkyl-N-hydroxyaminocarbonylalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, arylthio, aralkylthio, alkoxycarbonyl, aminocarbonyl, alkoxycarbonylamino, cycloalkyl, bicycloalkyl, bicycloalkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, heterocycloalkoxycarbonyl, heteroaryloxycarbonyl, heteroaralkoxycarbonyl, groups.

Where the term "alkyl" is used anywhere in the specification, either alone or within other terms such as "haloalkyl", "hydroxyalkyl", " alkylthio", "alkylsulfonyl" etc. it includes linear or branched radicals having one to ten carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to six carbon atoms. Examples of such radicals include but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, isohexyl, heptyl, octyl etc. The term "alkenyl" includes linear or branched radicals having at least one carbon-carbon double bond of two to ten carbon atoms or, preferably, two to six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" includes radicals wherein any one or more of the alkyl carbon atoms is substituted with halogen atoms as defined above. Examples include monohaloalkyl, dihaloalkyl, polyhaloalkyl and similar radicals. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. The alkyl group in haloalkyl group is a lower alkyl group and is termed lower haloalkyl group. "Lower haloalkyl" includes radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloroethyl, pentafluoroethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, and the likes. The term "hydroxyalkyl" includes linear or branched alkyl radicals having one to ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl.

The terms "alkoxy" and "alkoxyalkyl" includes linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. Preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also includes alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one

or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl, methoxypropyl and the like. The "alkoxy" or "alkoxyalkyl" radicals may further contain substitution consisting of one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and the like.

The term "aryl", alone or in combination, includes carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" includes saturated, partially saturated and unsaturated ring-shaped radicals, the heteroatoms selected from either nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 7-membered heteromonocyclic group containing one or more heteroatoms selected from N, O and S. Examples of such groups include but not limited to aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxazepinyl, thiazepinyl, oxazolidinyl, thiazolidinyl and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole and the like; the term "heteroaryl" includes unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic group containing one or more heteroatoms selected from O, N, S. Example of such groups include but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-tetrazolyl etc.), indolyl, isoindolyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl, pyranyl, 2-furyl, 3-furyl, benzoxazolyl, benzoxadiazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, benzothiadiazolyl and the like. The term also includes radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The aforesaid "heterocyclic group" may have 1 to 4 substituents such as lower alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, hydroxy, oxo, amino and lower alkylamino, lower alkoxy, halo, lower thioalkyl, acyl,

acylamino groups. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals and more preferably examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, pthalazinyl, quinazolinyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzothiazolyl, and the like.

The term "sulfonyl", used alone or in combination with other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" includes alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are lower alkylsulfonyl radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "arylsulfonyl" includes aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The terms "alkanoyl" or "acyl" include radicals derived from carboxylic acids and include but not limited to substituted or unsubstituted groups selected from formyl, acetyl, propionyl (propanoyl), butanoyl (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl, benzoyl or the like. The term "carbonyl" used either alone or with other terms, such as "alkylcarbonyl", denotes - (C=O)-. The term "alkylcarbonyl" includes radicals having a carbonyl radical substituted with an alkyl radical such as acyl or alkanoyl described above. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" includes alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" includes radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms for example

methoxycarbonylmethyl, tert-butoxycarbonylethyl, and methoxycarbonylethyl. The term "aminocarbonyl" when used separately or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", substituted or unsubstituted. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "amidino" denotes an -C(=NH)-NH_2 radical. The term "cyanoamidino" denotes an -C(=N-CN)-NH_2 radical. The term "heterocyclicalkyl" includes heterocyclic-substituted alkyl radicals. More preferred heterocyclicalkyl radicals are "lower heterocyclicalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl, pyridylmethyl and thienylmethyl. The term "aralkyl" includes aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, diphenylethyl and the like. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, acylamino, alkoxycarbonyl, alkylthio and the like. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" includes radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term "cycloalkenyl" includes unsaturated cyclic radicals having three to ten carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and the like. The term "alkylthio" includes radicals containing a linear or branched alkyl radical attached to a divalent sulfur atom. Example of alkylthio are methylthio (CH_3-S-), ethylthio, butylthio, and the like. The term

"alkylsulfinyl" includes radicals containing a linear or branched alkyl radical attached to a divalent-S(=O)-atom.

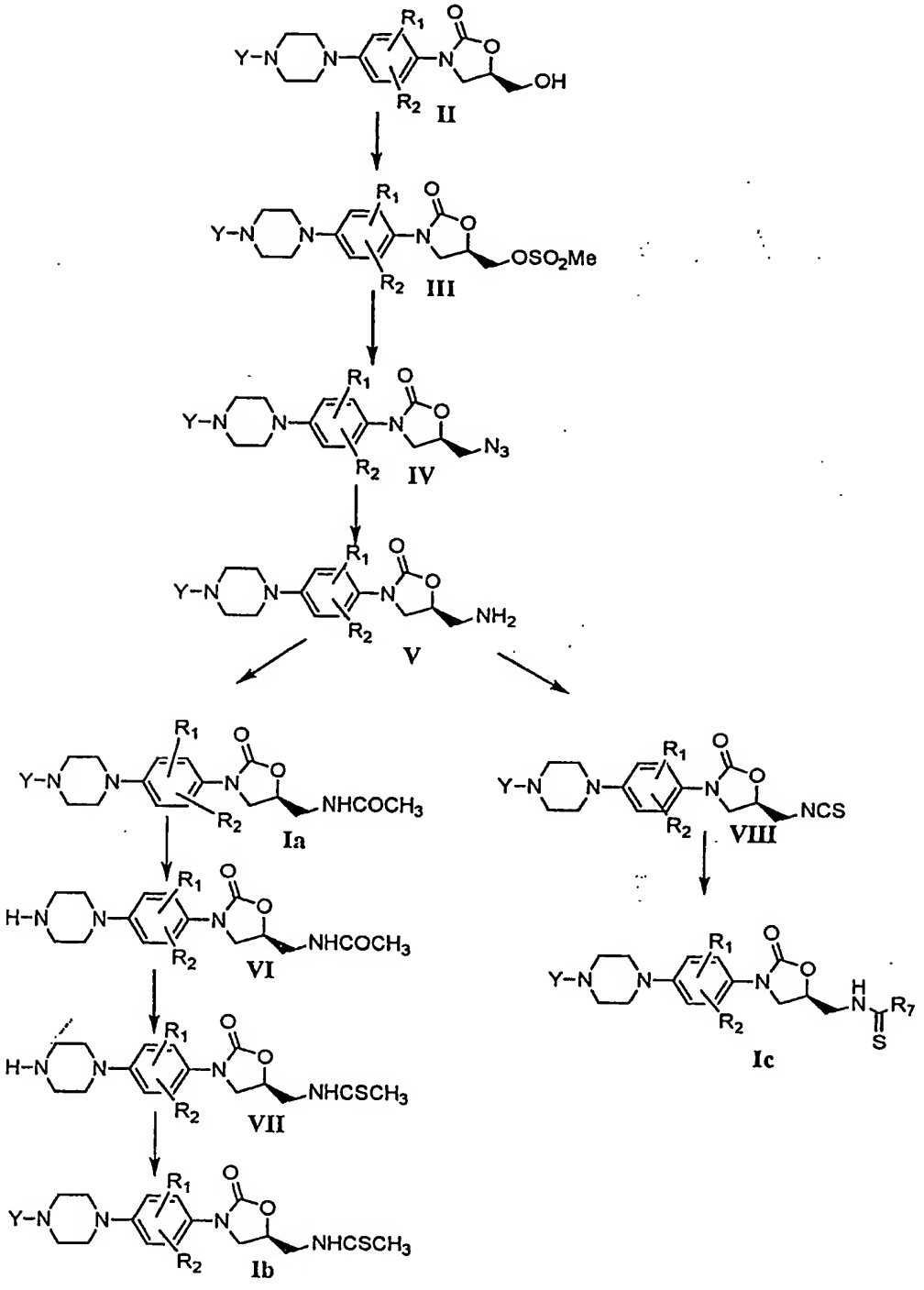
The term "aminoalkyl" includes alkyl radicals substituted with amino radicals. Preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" includes aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. Preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The terms "N-alkylamino" and "N-N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical. The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical; respectively, to an amino group. The terms "N-arylaminoalkyl" and "N-aralkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aralkyl radical, respectively, and having the amino group attached to an alkyl radical. Preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The terms "N-alkyl-N-arylaminoalkyl" and "N-aralkyl-N-alkylaminoalkyl" denotes N-alkyl-N-arylamino and N-alkyl-N-aralkylamino groups, respectively, and having the amino group attached to alkyl radicals. The term "acyl", whether used alone, or with another term such as "acylamino" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" includes an amino radical substituted with an acyl group. Examples of an "acylamino" radical is acetylamino or acetamido ($CH_3C(=O)$-NH-) where the amine may be further substituted with

alkyl, aryl, or aralkyl. The term "arylthio" includes aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The term "aralkylthio" includes aralkyl radicals as described above, attached to a divalent sulfur atom. An example of "aralkylthio" is benzylthio. The term "aryloxy" includes aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The term "aralkoxy" includes oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. Preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The term "haloaralkyl" includes aryl radicals as defined above "carboxyhaloalkyl" includes carboxyalkyl radicals as defined above having halo radicals attached to the alkyl portion. The term "aralkenyl" includes aryl radicals attached to alkenyl radicals having two to en carbon atoms, such as phenylbutenyl, and phenylethenyl or styryl.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

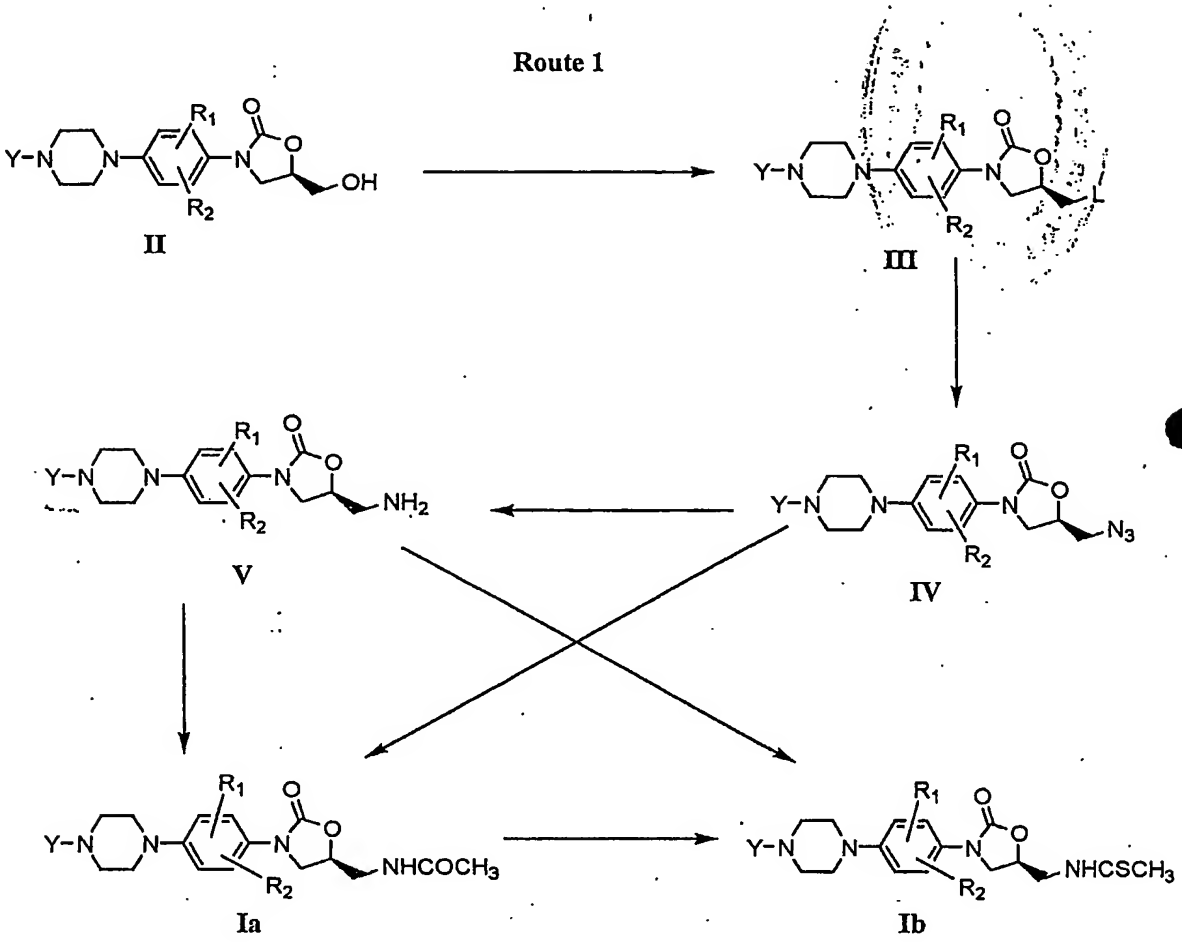
The compounds of general formula (I) may be prepared by one or more routes or combinations of reactions outlined in the following scheme. The method comprises:

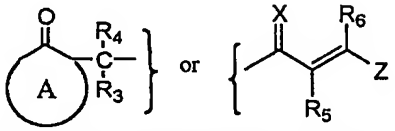
SCHEME


Y-N
N
R1
R2
O
O
N
OH
II
OSO2Me
III
N3
IV
NH2
V
NHCOCH3
Ia
H-N
VI
NHCSCH3
VII
Ib
NCS
VIII
Ic
S

The compounds as described in the scheme above may be prepared as described in the following sections:

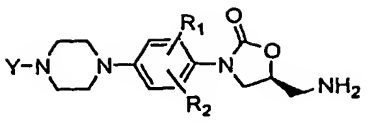
Route 1



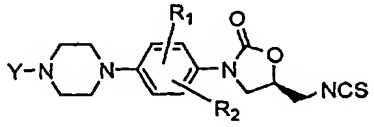
Where Y =  or

L = leaving group such as mesylate, tosylate, halogen etc.

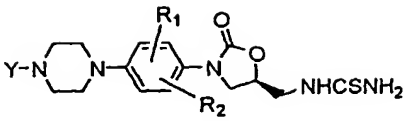
Route 2



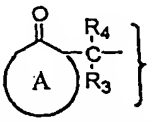
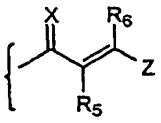
V



VIII

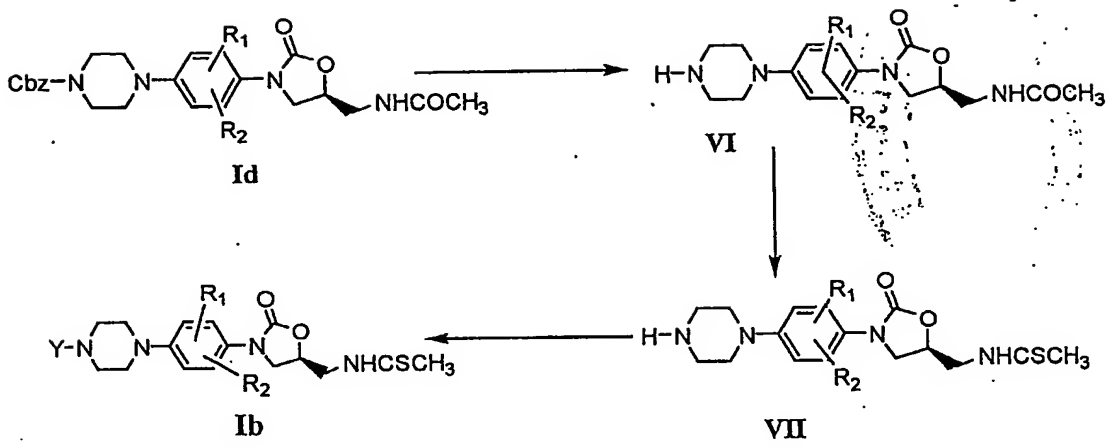


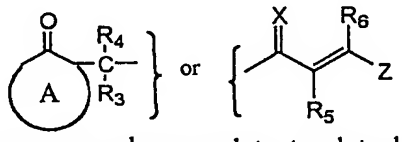
Ic

Where Y =  or 

L = leaving group such as mesylate, tosylate, halogen etc.

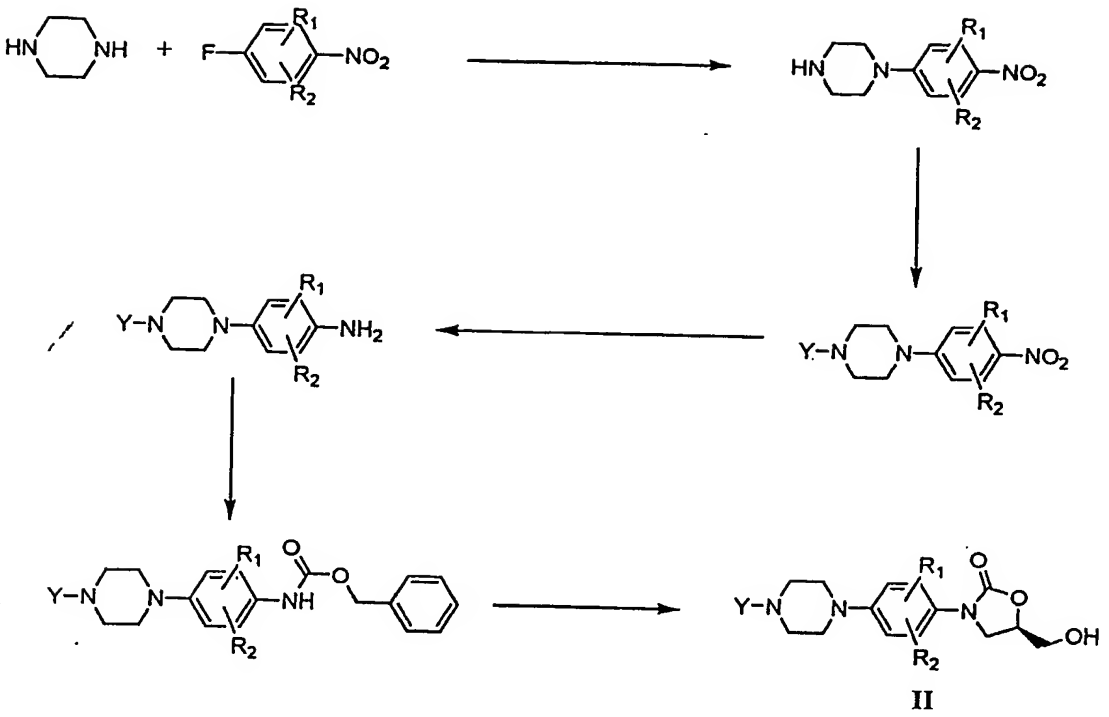
Route 3



Where Y = 

L = leaving group such asmesylate, tosylate, halogen etc.

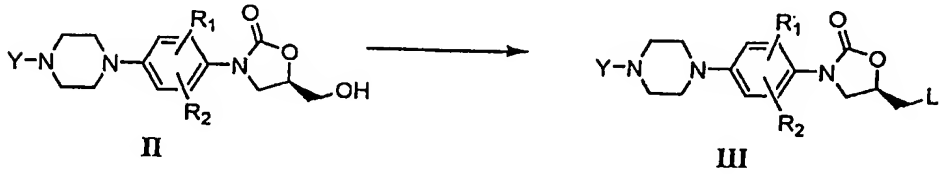
Route 4



II

The reactions described in the routes 1-4 outlined above may be performed by using the methods described herein:

Route 1

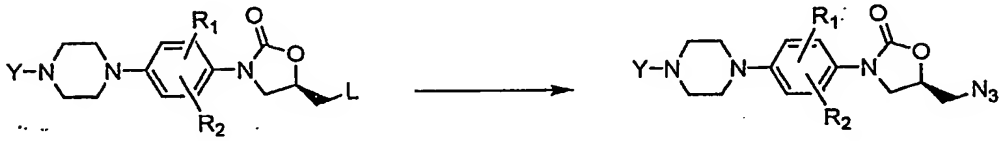


II III

Compounds of general formula III may be obtained by treating the compounds of general formula II, with appropriate sulfonyl chloride such as p-Ts-chloride, MsCl, benzene sulfonyl chloride and the like to get sulfonyl esters in presence of bases like triethylamine, pyridine,

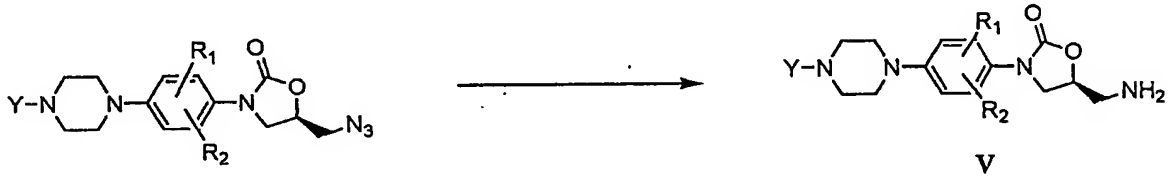
K_2CO_3 and the like or mixture thereof. Solvents such as DMF, DMSO, dichloromethane, dichloroethane, pyridine and the like and the mixtures thereof may be used. The temperature may range from 0 °C to reflux temperature of the solvent, preferably between 5 °C to 40 °C.

Alternatively, the compounds of general formula III, where L is halide, may be obtained by treating the compounds of general formula II with $SOCl_2$, $POCl_3$, PCl_5, PBr_3 and the like, HBr/red P, in the presence of solvents such as DMF, DMSO, THF, benzene, CH_2Cl_2, DCE and the like. The temperatures may range from 0 °C to 50 °C. The mole ratio of halogenating agent to compounds II can range from 1:1 to 1:1.5.



III IV

Compounds of general formula IV may be obtained by treating the compounds of general formula III with metal azides in solvents such as DMSO, pyridine, DMF and the like may be used. Temperature in the range of temperature 50 °C to 120 °C may be used, preferably between 30 °C to 60 °C.



IV V

Compounds of general formula V can be obtained by reducing the compounds of general formula IV with Pd/C and H_2 at pressures ranging from 10 to 20 psi at room temperature. Alternatively they can also be prepared by triphenylphosphine and NH_3 at ambient temperature. The molar ratio of compounds IV and reducing agent can range from 1:10 to 1:25.

V Ia

Compounds of general formula Ia can be obtained by treating the compounds of general formula V with pyridine and acetic anhydride preferably at low temperature in solvents such as THF and diethylether under anhydrous conditions. Other acylating agents, bases and solvents may be used to get appropriate acyl group.

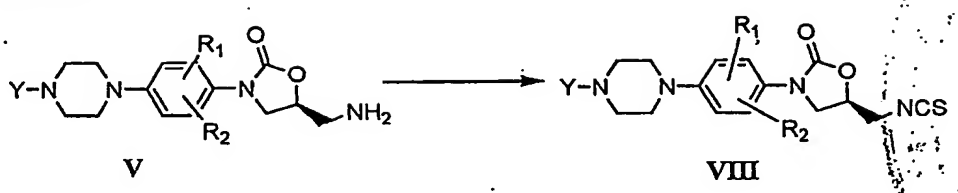
V Ib

Compounds of general formula **Ib** may be obtained from compounds of general formula V by treating it with ethyl thioacetate in presence of bases such as NaOH, KOH, and metal fluorides preferably NaF at ambient temperature for 2-5 hours using solvents such as methanol, diisopropyl alcohol, t-butanol or ethyl alcohol.

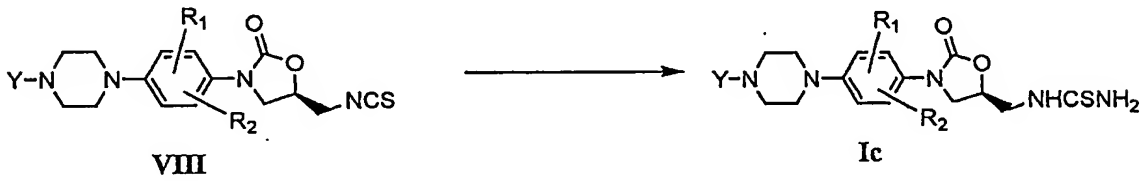
Ia Ib

Compounds of general formula **Ib** may be optionally obtained from compounds of general formula Ia by treating it with Lawesson's reagent in 1,4-dioxane.

Route 2

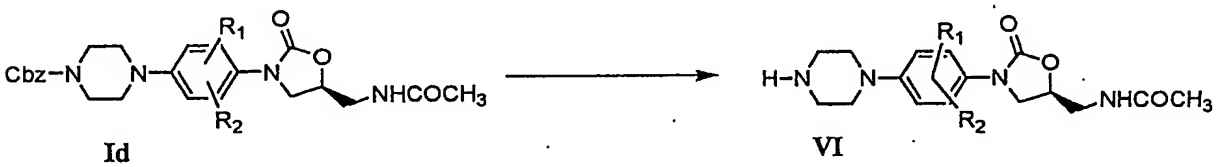


Compounds of general formula VIII can be obtained from compounds of general formula V by treating with carbon disulfide solution in presence of bases such as TEA & pyridine employing catalytic amount of esters of halogenated formic acid at temperatures between 0 °C and 50 °C depending upon the choice of bases.

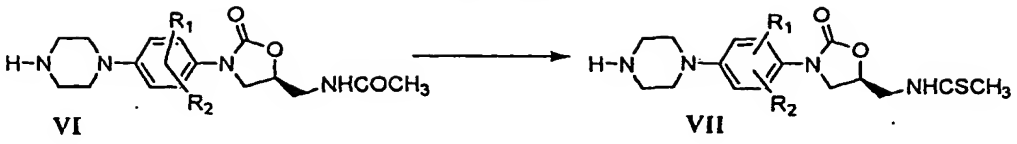


Compounds of general formula Ic may be obtained from compounds of general formula VIII by treating it with ammonia at temperatures ranging between –10 °C to 50 °C.

Route 3

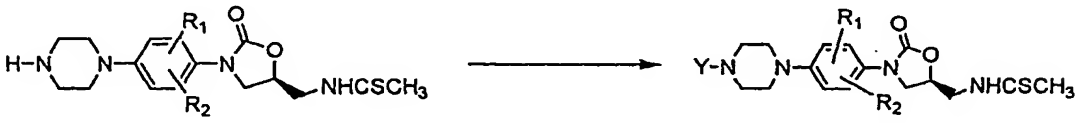


Compounds of general formula VI may be obtained by treatment of compounds of general formula Id with trifluoroacetic acid or Pd/C and ammonium formate in formic acid or hydrogenation of compounds of general formula Id using Pd/C under atmospheric pressure.



VI VII

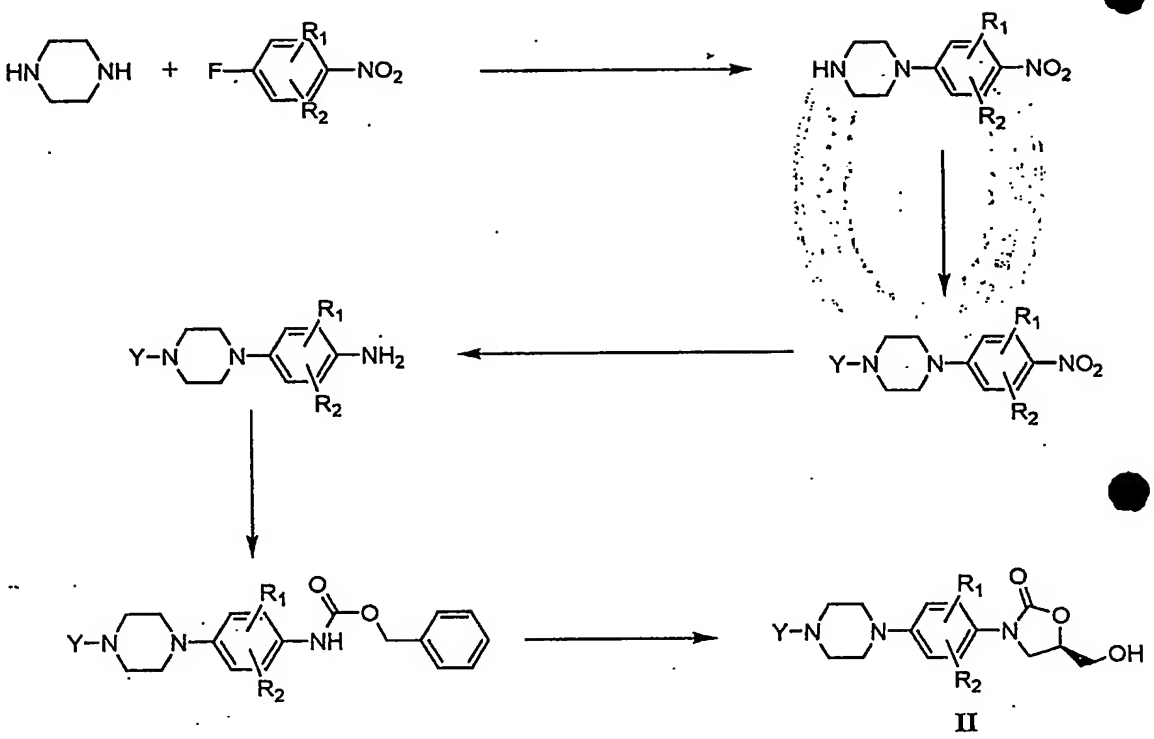
Compounds of general formula **VI**, when treated with P_2S_5 in the presence of Na_2CO_3 or K_2CO_3 in solvents such as DCE or DMC and the like to afford compounds of general formula **VII**. The reaction may also be achieved by treating compounds of general formula **VI** with Lawesson's reagent.



VII Ib

Compounds of general formula **Ib** may be obtained from compounds of general formula VII by coupling it with Y employing different sets of coupling agents depending upon the choice of nature of Y. The coupling agents can be selected from any of the sets described below: formaldehyde or paraformaldehyde or 15% HCl in methanol and ethereal HCl (ii) acid chloride corresponding to Y, bases such as K_2CO_3, Na_2CO_3 and catalytic amount of HCl or DCC, HOBT etc.

Route 4



II

Piperazine and substituted fluoronitrobenzene can be coupled by just heating them together in solvents like EtOAc, THF, acetonitrile. The condensed product obtained thus is treated with Y as described in the transformation of **VII** to **Ib**. Then the coupled product is reduced employing reducing agents such as LAH, Sn/HCl or Hydrazine hydrate in Raney Ni and the like. The aniline obtained is then treated with benzyl chloroformate in the presence of bases like alkali metal carbonates or alkali. The chiral oxazolidinone ring can be formed after treating the CbZ carbamate compound with bases such as n-BuLi followed by (R)-glycidyl butyrate to afford compounds of general formula **II**. Reaction conditions suitable for organometallic reactions are employed such as non protic solvents, inert atmosphere and the like.

Pharmaceutically acceptable salts means salts formed by the addition of acids useful for administering the compounds of the present invention and includes hydrochloride, hydrobromide, sulfate phosphate, acetate, propionate, lactate, mesylate, ,maleate, succinate, tartarate, citrate, 2-hydroxyalkylsulfonate, fumarate and the like when a basic group is present on 5-substituent on the oxazolidinone ring.

These salts may be in hydrated form- some of the compounds of the invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal in such protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., 201-245 along with references therein.

It will be appreciated that the above-mentioned preparation of the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or pharmaceutically acceptable solvate thereof is a stereoselective procedure and that the compound of formula (I) is a single stereoisomer. Favorably, a compound of formula (I) The preferred configuration at C-5 of the oxazolidinone ring of compounds claimed in the invention is (s)-under the Caun-Ingold-Prelog nomenclature system. Since this (s)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (s)-enantiomers the difference lies in the fact that double as much racemic material will be required to produce the same antibacterial effect.

Preferably the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or pharmaceutically acceptable solvate thereof is in optically pure form.

The absolute stereochemistry of the compounds may be determined using conventional methods, such as X-ray crystallography.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: the Science and Practice of Pharmacy, 19th Ed., 1995. The compositions may be in the conventional forms, such as capsules, tablets, powders, solutions, suspensions, syrups, aerosols or topical applications. They may contain suitable solid or liquid carriers or in suitable sterile media to form injectable solutions or suspensions. The compositions may contain 0.5 to 20 %, preferably 0.5 to 10 % by weight of the active compound, the remaining being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

The compounds of Formula I are useful in the treatment of microbial infections in humans and other warm blooded animals, by either oral, topical or parenteral administration.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals including mammals, rodents, and the like. More preferred animals include horses, dogs and cats.

For the treatment of any of the above-mentioned diseases the compounds of formula (I) may be administered, for example, orally, topically, parenterally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is, the compounds of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating bacterial infections in humans and animals that have been diagnosed with having bacterial infections, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially active. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100 mg/kg, more preferably about 3.0 to about 50mg/kg of body weight/day. However, it should be appreciated that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection, and the particular compound being used. Also, it must be understood that the initial dosage administered may be increased beyond the upper level in order to rapidly achieve the desired blood level or the initial dosage may be smaller than the optimum and the and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also, be divided into multiple doses for administered, e.g. two to four times per day.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes as previously indicated, in single or multiple doses. More specifically, the novel compounds described in the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs,

syrups, and the like. The carriers may include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents etc. Moreover, for oral consumption, the pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds as described in the invention are present in the compositions at concentration levels ranging from 5% to 60% by weight, preferably 10% to 50% by weight.

For oral administration, the tablets may be combined with various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine along with various disintegrants such as starch more preferably corn, potato or tapioca starch, alginic acid, sodium carbonate and certain complex sillicates; together with binders like polyvinylpyrrolidone, sucrose, gelatin and acacia, humectants such as for example, glycerol; solution retarding agents, such as, for example paraffin; absorption accelerators such as, for example, quartenary ammonium compounds; wetting agents like cetyl alcohol and glycerol monostearate; absorbents like kaolin and bentonite clay. Additionally, magnesium stearate, sodium lauryl sulfate, talc, calcium stearate, solid polyethylene glycols and mixtures thereof are often added as lubricating agents for tabletting purposes. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Similar type of solid compositions may also be employed as fillers and excipients in soft and hard gelatine capsules; preferred materials includes lactose, milk sugar or high molecular weight polyethylene glycols.

The active compounds can also be in micro-encapsulated form using one or more of the excipients noted above. The solid dosage forms of tablets, dragees, capsules, pills, and the granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings which are well known in the field of pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with atleast one inert diluent such as sucrose, lactose and starch. They may also contain, additional substances for e.g. tableting lubricants and other substances like magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the formulation may also contain

powders can also be used as a medium of providing therapeutic dosages to the patients as will be necessary.

The ointments, pastes, creams and gels may, in addition to the active ingredient, contain excipients like animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, zinc oxide or their mixtures.

Powders and sprays may contain, in addition to the active substance, excipients like lactose, talc, silicic acid, aluminium hydroxide, calcium silicates and polyamide powder, or their mixtures. Sprays will additionally contain propellants like chlorofluorohydrocarbons.

The pharmaceutically acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro and against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically acceptable compounds of the present invention show activity against enterococci, pneumococci, and methicillin resistant strains of S.aureus and coagulase negative staphylococci, together with morganella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by microbroth dilution technique as per 0NCCLS standards.

The antibacterial properties of the compounds of the invention may also be demonstrated and assessed in vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm blooded mammal using standard techniques.

Dated this 30th day of March 2002

Signature

To
The Controller of Patents
The Patent Office,
at Mumbai

US 1050989204P1

Creation date: 08-22-2005
Indexing Officer: RZEFERE - RAHEL ZEFERE
Team: OIPEBackFileIndexing
Dossier: 10509892

Legal Date: 06-03-2005

No.	Doccode	Number of pages
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